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John M. Dietschy, M.D.

Clinical Endocrinology and Metabolism

Principles and Practice

David Rabin, M.D., F.R.C.P.

T. Joseph McKenna, M.D., F.R.C.P.I.

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David Rabin, M.D., F.R.C.P.

Professor of Medicine
Professor of Obstetrics and Gynecology
Director of The Section of Endocrinology
Vanderbilt School of Medicine
Nashville, Tennessee

T. Joseph McKenna, M.D., F.R.C.P.I.

Director of The Department of Endocrinology
St. Vincent's Hospital
Dublin, Ireland

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Foreword

There have been few more fruitful unions than that which has developed during the present century between basic science and clinical practice in the area of endocrinology. It has been said that some hormones are essential for life and that others make life worth living. Since hormones directly or indirectly affect every cell in the mammalian body, it is essential that every serious biologist and every physician should have a clear understanding of the nature of hormones, their effects, their mechanisms of action, and the normal and abnormal regulation of their secretion in health and disease.

In science, there are classical books that represent the best that is known at a particular time, setting it forth with memorable clarity and sound perspective. The book you are about to read is such a work. There are also books that are classical in the sense that they set forth for the first time seminal new concepts that are destined to influence the course of history. Sections of the book you hold are classical in this latter sense. But, in science, there can be no books that are definitive in the sense that they reveal all that is to be known about a subject, for science is a fabric woven of concepts that are forever undergoing modification and elaboration, requiring continual reweaving of the fabric. To use the words of Robert Browning, in science it can always be said, "The best is yet to be."

The current textbook has been written by two endocrinologists whose paths crossed at Vanderbilt University during the 1970s, at a time when they both were attaining the peaks of their academic capabilities after having worked in widely separate parts of the world.

The excellence of this textbook is a reflection of the broad and deep experience the authors have had in endocrinology. Both are well-grounded in basic science and both are superb clinicians. They know endocrinology well, in all of its aspects, from personal experience. Equally basic to the excellence of this textbook is the fact that both writers are superb teachers, who write living prose, embodying a combination of detailed knowledge, clarity, well-placed emphasis, and style that will make this book an unforgettable part of the education of every reader.

Grant W. Liddle, M.D.

Preface

The philosophy of the clinical practice of endocrinology and metabolism described in this text has evolved from our experience in day-to-day patient management. The material provides a thorough working knowledge of the physiology of the endocrine system, the basis from which familiarity with disease pathogenesis and symptomatology evolve. We emphasize practical clinical problems, examine the relative merits of available diagnostic procedures, and provide guidance for the most appropriate applications of various therapeutic options. Our goal is to provide a unified approach to endocrinology and metabolism with sufficient basic science and clinical awareness. We hope that the principles of clinical practice enunciated here will facilitate and enrich the reader's knowledge and understanding of the management of endocrine and metabolic disorders.

We acknowledge our teachers, colleagues, and students who have influenced our approach to the science and practice of endocrinology and metabolism. Foremost among these are Drs. John Eagar Howard and Kenneth L. Zierler of Johns Hopkins Medical Center, Baltimore, Maryland; Francis P. Muldowney of University College, Dublin; the late Larry Kyle of Georgetown University Medical Center, Washington, D.C.; and Grant W. Liddle of Vanderbilt School of Medicine, Nashville, Tennessee, who brought us together for happy and productive years in the Division of Endocrinology. We are indebted to our colleagues, postdoctoral fellows, medical house staff, and students for their stimulation and encouragement. The material in this text reflects all of these influences, and particularly the lessons diligently taught by the patients we have been privileged to treat.

The immediate preparation of this book has been aided by many. We are grateful for the helpful comments and criticisms given by those who reviewed sections during their preparation—Dr. Stanley Schwartz of Philadelphia, Drs. Rowan DeBold, Randy Linde, Brent Gooch, and Craig Sussman, all of Vanderbilt University School of Medicine, and Drs. D.K. O'Donovan, Francis P. Muldowney, Niall O'Higgins, Karina Butler, and Fergal Magee, all of Dublin. We are pleased to recognize the contributions of Mary Margaret Alsobrook Peel, who prepared many of the illustrations, and of our photographer, Dean Denis of Nashville. The special checking of references was conscientiously performed by Dana and Leora Rabin. We are happy to acknowledge the expert and enthusiastic secretarial assistance of Eileen Reid in Dublin and of Patty Adams, Bettye Ridley, Marion Gains and Pat Runsvold in Nashville. The courteous and ready assistance provided by our editors at Grune and Stratton in New York greatly eased the pressures associated with the completion of this volume.

David Rabin, M.D.
T. Joseph McKenna, M.D.

Contents

GENERAL FEATURES OF THE ENDOCRINE SYSTEM

Some Endocrinological Principles

The endocrine system includes all groups of cells that secrete directly into the bloodstream and lymphatics and is in contrast to exocrine glands such as the gall bladder, the mammary and salivary glands whose secretions are conducted along ducts. Hormones are the physiologically active products of endocrine glands. The endocrine system has traditionally included a series of well-defined glands: the hypophysis, thyroid, parathyroids, adrenals, pancreatic islets, ovaries, and testes. It is clearly established, however, that many organs not classically considered to be endocrine glands contain groups of cells that synthesize hormones and under certain conditions secrete these into the bloodstream. Later in this chapter, "eutopic" and "ectopic" production of hormones will be further considered.

The vascular and lymphatic systems are the common channels whereby hormones influence metabolic processes. The output of the endocrine system is, for the most part, not confined by internal anatomic boundaries, but gains access to and potentially can influence most organs, tissues, and cells; hence, Fuller Albright's statement that endocrinology is an indivisible division of internal medicine.[1] An essential prerequisite for responsiveness of a cell to a hormone is the presence of a specific receptor for the hormone, either on the cell surface or within the cytoplasm of the cell. Hormones fall into two main classes: (1) steroids and thyronines, which are lipid soluble; and (2) polypeptides and catecholamines, which are water soluble. Steroid hormones are produced by endocrine glands of mesodermal origin (the adrenal cortex and the gonads), whereas polypeptides, catecholamines, and thyronines are secreted by glands of ectodermal or neuroectodermal origin. Hormones circulate in extremely small concentrations; for example, insulin and human growth hormone are present in blood in concentrations of only a few nanograms (ng)/ml of plasma. That is of the order of $10^{-11}M$. Metabolic effects can be produced by as little as $10^{-8}M$ of insulin per gram of muscle or adipose tissue in vivo.

The ability of the cell to select out a particular hormone circulating in such low concentration is dependent upon the presence of specific *receptors* for the hormone, either on the cell surface or within the cytoplasm. The receptor thus serves as a means of recognition between the cell and a circulating hormone. The dynamic role of receptors in modulating the action of hormones will be discussed later. For the present, consider the hypothetical cell shown in Figure 1. The cell can take up various substances from, and release the same or other substances into, its immediate environment. Uptake and release are highly specific and are dependent upon the presence of specific carriers (for example, for sugar transport) and may require the expenditure of energy by the cell, that is the use of adenosine 5′-triphosphate (ATP). The cell has or can synthesize the enzymatic machinery to dissimilate materials along various pathways. These may be either catabolic, such as the combustion of carbohydrate or fat to carbon dioxide and water, or anabolic, such as the incorporation of amino acid into protein. It has long been an endocrine axiom that hormones do not initiate metabolic processes within the cell, but do alter their rates of reaction.

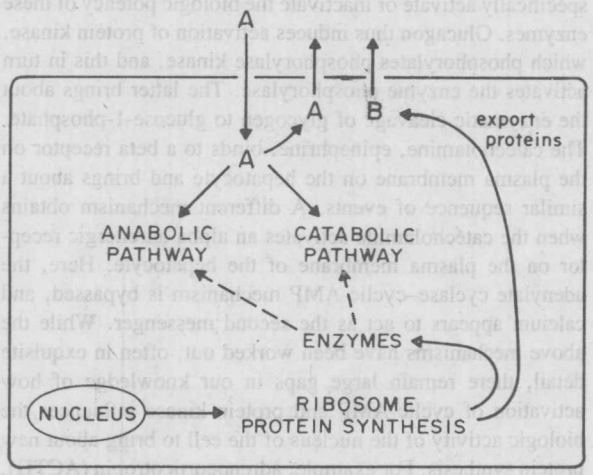

Fig. 1. Schematic representation of the cell and some of its important activities. Substances are taken up by the cell and may subsequently undergo conversion via either catabolic or anabolic pathways. Enzymes, catalyzing these pathways, are synthesized in the cell directed by the nucleus. The cell may export substances, which it itself has synthesized, or it may release substances, which it has previously taken up from its environment.

Molecular Basis of Hormone Action

Hormones influence cellular metabolic processes either directly or indirectly, for example, by promoting the synthesis of one or a family of growth factors. As a generalization, the combination of a hormone with its receptor brings about changes within the cell by one of two mechanisms: (1) the generation of a second messenger within the cell; or (2) the translocation of the hormone–receptor complex into the nucleus, where the complex initiates changes within the chromatin, resulting in production of messenger RNA, and in turn initiating new protein synthesis by the cell. In general, polypeptide hormones and catecholamines appear to act via the former mechanism following interaction of hormone with its receptor at the cell surface. Steroids in the main are freely permeable to the cell membrane and exert their effects via the second mechanism.

Certain principles of the so-called "second messenger hypothesis" will now be examined more closely. As an example, turn to the interaction of glucagon with the liver cell membrane (Fig. 1). Specific binding of glucagon to its receptor is coupled with the activation of a membrane-bound enzyme, adenylate cyclase. This coupling mechanism is complex and requires the interaction of guanosine 5′-triphosphate (GTP) and other macromolecules. Activation of adenylate cyclase brings about the catalysis of ATP to adenosine 3′:5′-cyclic phosphate (cyclic-AMP). The latter binds to the regulatory subunit of protein kinase, thereby liberating the catalytic subunit of this enzyme. This in turn initiates the phosphorylation of certain key enzymes that, pari passu, either specifically activate or inactivate the biologic potency of these enzymes. Glucagon thus induces activation of protein kinase, which phosphorylates phosphorylase kinase, and this in turn activates the enzyme phosphorylase. The latter brings about the enzymatic cleavage of glycogen to glucose-1-phosphate. The catecholamine, epinephrine, binds to a beta receptor on the plasma membrane on the hepatocyte and brings about a similar sequence of events. A different mechanism obtains when the catecholamine activates an alpha-adrenergic receptor on the plasma membrane of the hepatocyte. Here, the adenylate cyclase–cyclic-AMP mechanism is bypassed, and calcium appears to act as the second messenger. While the above mechanisms have been worked out, often in exquisite detail, there remain large gaps in our knowledge of how activation of cyclic-AMP and protein kinase influences the biologic activity of the nucleus of the cell to bring about new protein synthesis. For example, adrenocorticotropin (ACTH), acting on the adrenal, and luteinizing hormone (LH), acting on the Leydig cell, initiate an increase in steroidogenesis associated with the activation of one or several enzymes of the steroidogenic pathway. The intermediary steps whereby cyclic-AMP brings about an increase in 20,22-cholesterol-lyase activity remain unclear. Similarly, cyclic-AMP initiates an increase in human chorionic gonadotropin (HCG) synthesis by trophoblastic tumor cell lines, a process which involves the mediation of the nucleus and new protein synthesis. Again, the detailed biochemical steps whereby this process is accomplished remain obscure. It is believed that insulin and prolactin also act via production of second messengers by the cell. Prolactin binds to a specific receptor and brings about an increase in protein kinase without a concomitant activation of adenylate cyclase. The putative second messenger for insulin has eluded identification, but, at the time of writing, several laboratories appear to agree that it is a small polypeptide fragment cleaved off the cell membrane following interaction of insulin and its receptor. This second messenger may be responsible for both the membrane and the intracellular metabolic effects of insulin. Kono has suggested that the insulin second messenger brings about translocation of a carrier from an intracellular locus to the cell membrane.[2] This leads to profound changes in the properties of the cell membrane (e.g., enhancement of D-glucose transport) and dramatic changes in the flux of certain ions, such as potassium. The putative second messenger of insulin thus has diverse effects, which are cumulatively anabolic, on the intermediary metabolism of the cell.

Steroid-mediated changes in cell physiology are brought about in general by interaction between the hormone and its receptor, which is located in the cytosol (Fig. 2). The hormone–receptor complex is then translocated to the nucleus where it binds specifically to a locus on the chromatin, activating RNA polymerase, with ultimate synthesis of one or several specific messenger RNAs. These products leave the nucleus and travel to the ribosome where they direct the synthesis of one or a family of proteins. The ability of the steroid to activate the genome thus permits the appearance of specific gene products, which are either utilized intracellularly or which may be exported. Two characteristics of this mode of hormone action are: (1) a delay in the generation of the hormonal effects; and (2) inhibition of hormonal action by agents (such as actinomycin) that block DNA-directed RNA synthesis.

THE RELATIONSHIP BETWEEN HORMONES AND GROWTH FACTORS

In addition to what are classically referred to as hormones, whose sites of synthesis are recognized, there have been identified an increasing number of so-called "growth factors." Certain growth factors were initially recognized in serum, and some are clearly dependent for adequate synthesis on the presence of a trophic hormone. Take as an example the insulin-like growth factors (IGF) I and II, whose structures have been determined, and trace their history. The resolution of this problem has its genesis in two apparently discrete sets of findings: first, the presence in plasma of biologic activity resembling that of insulin, but which could not be suppressed by addition of anti-insulin antiserum. Methods were evolved for the extraction of so-called "soluble nonsuppressible insulin-like activity" (NSILA) by Froesch, Humble, and their colleagues.[3] Concurrently, it was recognized that the powerful effects of growth hormone observed in vivo were absent under in vitro conditions. The second set of findings commenced

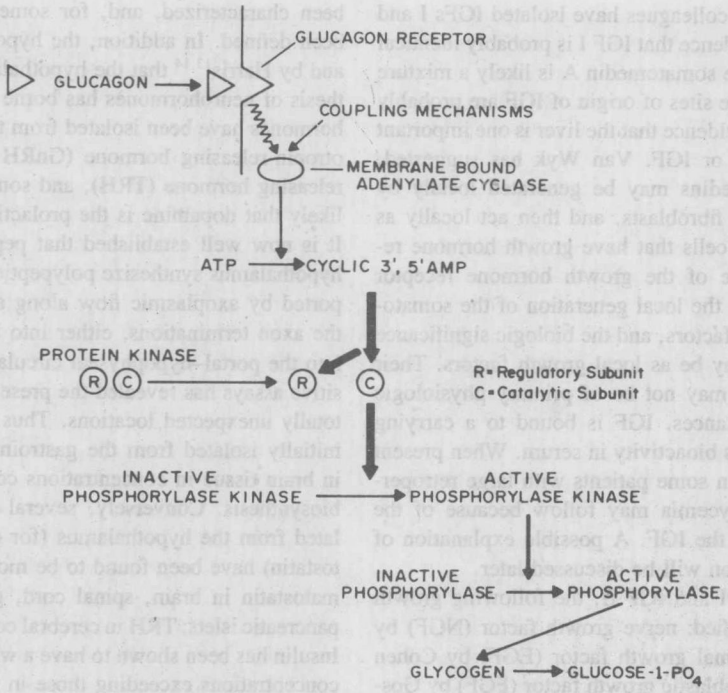

Fig. 1. Schematic representation of the action of the polypeptide hormone, glucagon. Glucagon interacts with a specific receptor on the cell membrane, and this is coupled to the adenylate cyclase system. Activation of the latter results in the production of cyclic-AMP, which in turn stimulates protein kinase. The latter results in the phosphorylation of a series of enzymes, culminating in the activation of phosphorylase, which catalyzes the conversion of glycogen to glucose-1-phosphate.

with the classical studies by Salmon and Daughaday.[4] They established that injection of the growth hormone into experimental animals was followed by the appearance in serum of a substance that increased the incorporation of radioactive sulfate into mucopolysaccharide–protein complexes of rat cartilage. Hall et al.[5] and Van Wyk et al.[6] developed methods for extraction of the so-called "sulfation factor" (SF) from plasma. It became apparent that the SF, now renamed "somatomedin" and subdivided into A, B, and C fractions, possessed insulin-like activity under in vitro conditions and furthermore could compete for binding to the insulin receptor in several in vitro membrane systems. Purification of NSILA and somatomedin C was followed by the generation of antibodies and the development of radioimmunoassays for these

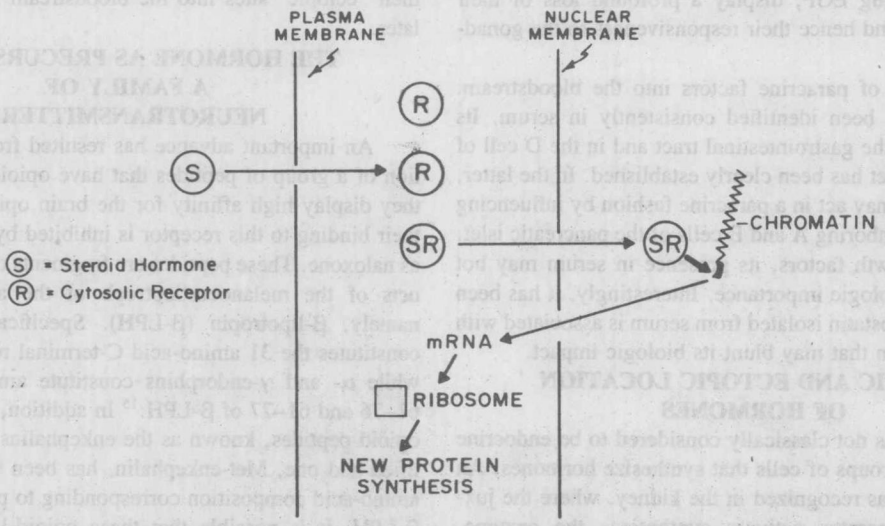

Fig. 2. Schematic representation of the interaction of a steroid hormone with the cell. The steroid hormone enters the cytoplasm of the cell where it interacts with a specific receptor. The steroid–receptor complex is then translocated to the nucleus where it results in the activation of messenger RNA, which exits the nucleus and initiates new protein synthesis in the cytosol.

factors. Froesch and his colleagues have isolated IGFs I and II and have provided evidence that IGF I is probably identical to somatomedin C, while somatomedin A is likely a mixture of IGF I and IGF II.[4] The sites of origin of IGF are probably multiple; there is good evidence that the liver is one important source of somatomedin or IGF. Van Wyk has suggested, however, that somatomedins may be generated locally by many tissues, including fibroblasts, and then act locally as growth factors in many cells that have growth hormone receptors. The importance of the growth hormone receptor would be that it triggers the local generation of the somatomedin family of growth factors, and the biologic significance of the somatomedins may be as local growth factors. Their presence in serum thus may not be of primary physiologic importance in most instances. IGF is bound to a carrying protein that may blunt its bioactivity in serum. When present in excess, however (as in some patients with large retroperitoneal tumors), hypoglycemia may follow because of the "insulin-like effects" of the IGF. A possible explanation of this interesting association will be discussed later.

In addition to IGF I and IGF II, the following growth factors have been identified: nerve growth factor (NGF) by Levi-Montalcini, epidermal growth factor (EGF) by Cohen and colleagues, and fibroblastic growth factor (FGF) by Gospodarowicz.[7–9] These are the forerunners of a family of growth factors that exert trophic influences primarily on one set of tissues, but often have far wider biologic effects. For example, EGF exerts important trophic influences on the epidermis, including the cornea. Epidermal growth factor also enhances the rate of growth of fibroblasts in culture, however, and elucidation of its mechanism of action may shed light on fundamental factors involved in cell differentiation and growth. The placenta is rich in EGF receptors, and EGF has been shown to enhance synthesis and release of both HCG and progesterone from a trophoblastic tumor cell line.[10,11] In addition, Ascoli has made the important observation that Leydig cells derived from a mouse tumor, when grown in culture medium containing EGF, display a profound loss of their HCG receptors and hence their responsiveness to the gonadotropin.[12]

"Overflow" of paracrine factors into the bloodstream: somatostatin has been identified consistently in serum. Its identification in the gastrointestinal tract and in the D cell of the pancreatic islet has been clearly established. In the latter, the polypeptide may act in a paracrine fashion by influencing secretion of neighboring A and B cells of the pancreatic islet. As with the growth factors, its presence in serum may not be of primary biologic importance. Interestingly, it has been noted that somatostatin isolated from serum is associated with a carrying protein that may blunt its biologic impact.

EUTOPIC AND ECTOPIC LOCATION OF HORMONES

Many organs not classically considered to be endocrine glands contain groups of cells that synthesize hormones. An early example was recognized in the kidney, where the juxtaglomerular apparatus actively synthesizes the enzyme, renin, which it secretes into the renal–venous bloodstream. During the last decade, the gastrointestinal tract has emerged as the source of numerous hormones. Many of these have been characterized, and, for some, physiologic roles have been defined. In addition, the hypothesis advanced by Dale and by Harris[13,14] that the hypothalamus was the site of synthesis of neurohormones has borne considerable fruit. Three hormones have been isolated from the hypothalamus [gonadotropin-releasing hormone (GnRH or LHRH), thyrotropin-releasing hormone (TRH), and somatostatin], and it is very likely that dopamine is the prolactin-inhibiting factor (PIF). It is now well established that peptidergic neurones of the hypothalamus synthesize polypeptides, which are then transported by axoplasmic flow along axons and are released at the axon terminations, either into the general circulation or into the portal–hypophyseal circulation. Availability of sensitive assays has revealed the presence of many hormones in totally unexpected locations. Thus, many of the hormones, initially isolated from the gastrointestinal tract, are present in brain tissue in concentrations concordant with their local biosynthesis. Conversely, several hormones originally isolated from the hypothalamus (for example TRH and somatostatin) have been found to be more widely distributed: somatostatin in brain, spinal cord, gastrointestinal tract, and pancreatic islets; TRH in cerebral cortex and pancreatic islets. Insulin has been shown to have a wide distribution with brain concentrations exceeding those in plasma often by an order of magnitude or greater. The role of hormones in the brain in what would traditionally be termed "ectopic loci" remains to be defined. An attractive hypothesis is their utilization as neurotransmitters. Human chorionic gonadotropin has traditionally been considered to be a unique product of the trophoblast. It has now been identified in most normal tissues, including the testis, pancreas, and gastrointestinal tract. The presence of hormones in diverse locations complicates a previously clear designation of hormones as either eutopic or ectopic. Of importance is that the presence of the hormone, e.g., insulin or HCG, inside a cell is not necessarily associated with its export from the cell into the peripheral circulation.

The consequences of secretion of these hormones from their "ectopic" sites into the bloodstream will be discussed later.

THE HORMONE AS PRECURSOR TO A FAMILY OF NEUROTRANSMITTERS

An important advance has resulted from the identification of a group of peptides that have opioid actions; that is, they display high affinity for the brain opium receptor, and their binding to this receptor is inhibited by antiopioids such as naloxone. These peptides are fragments of one of the products of the melanocorticotroph of the anterior pituitary, namely, β-lipotropin (β-LPH). Specifically, β-endorphin constitutes the 31 amino-acid C-terminal residue of β-LPH, while α- and γ-endorphins constitute amino-acid residues 61–76 and 61–77 of β-LPH.[15] In addition, a further class of opioid peptides, known as the enkephalins, have been identified and one, Met-enkephalin, has been shown to have an amino-acid composition corresponding to positions 61–65 of β-LPH. It is possible that these opioid-like peptides may derive from the cleavage of β-LPH, and/or they may be synthesized de novo in the hypothalamus, in the brain, and in posterior horn cells of the spinal cord.